TOUGH® 45 WP
CFR 40 SECTION 158 DATA REQUIREMENTS
SUMMARY OF STATUS

O-1 61-1 to 64-1, PRODUCT CHEMISTRY:

Please Note: In response to a letter from Gilmore, July 14, 1987, requesting the status of Section 158.120 Product Chemistry for both Tough® 3.75 EC and Tough® 45 WP the Agency confirmed in their letter of October 1, 1987 that the only comments by the reviewing branches concerned the original Confidential Statement of Formula for Tough® 45 WP and one of the inert ingredients in that formulation. Those concerns have been resolved and it is now assumed by the registrant that all requirements for Product Chemistry are satisfied for both products.

O-2 81-1, ACUTE ORAL LD50, RAT:

Two studies utilizing Pyridate technical as the test article were submitted 1/17/85. The studies, accession number 73280, were reviewed and classified as core guideline on 2/12/86. The resulting LD50's were: 1.) for Pyridate Technical: Males - 5993 mg/kg; Females - 3544 mg/kg; Both sexes - 4690 mg/kg, 2.) for Tough® 45 WP: Males - 2205 mg/kg; Females - 2377 mg/kg: both sexes - 2330 mg/kg.

O-3 81-2, ACUTE DERMAL LD50, RABBIT:

The following acute dermal toxicity studies were submitted by the registrant on January 17, 1985:

1. ACUTE DERMAL TOXICITY (LD50) STUDY WITH PYRIDATE TECHNICAL IN RABBITS, Project 037001, RCC, October 19,1984.
Based on the observations the LD50 for Pyridate technical in rabbits was determined to be > 2000 mg/kg.

2. ACUTE DERMAL TOXICITY (LD50) STUDY WITH LENTAGRAN WP (Tough® 45 WP) IN RABBITS, Project 036988, RCC, November 19,1984.
Based on the observations the LD50 dermal for the test article was determined to be > 2000 mg/kg.

The studies were assigned accession number 73280, reviewed by the Agency on February 12, 1986, and classified as Core-Guideline.

O-4 81-3, ACUTE INHALATION LC50, RAT:

The following acute inhalation studies were submitted by the registrant on January 23, 1984:

1. ACUTE INHALATION TOXICITY IN RATS, 4-HOUR EXPOSURE TO THE DUST OF CL 11.344 WP (Tough^{R} 45 WP), LNZ 24/78602, Huntingdon Research Centre, July 20, 1978.
Rats were exposed to a maximum attainable level of the dust of Tough^{R} 45 WP (2.14 g/cubic meter) for a single period of 4 hours. On this basis it was calculated that acute inhalation exposure to Tough^{R} 45 WP would present little hazard.

2. FOUR HOUR AEROSOL INHALATION TOXICITY STUDY (LC50) WITH PYRIDATE TECHNICAL IN RATS, Project 016255, RCC, May 1983.
The acute 4-hour inhalation toxicity of Pyridate technical in rats of both sexes observed over a period of 14 days was estimated to be >4370 mg/cbm air. Due to technical difficulties, the exposure to a higher concentration was not possible.

The studies were assigned accession number 73280, reviewed on February 12, 1986 and classified as Core-Minimum.

O-5 81-4 PRIMARY EYE IRRITATION, RABBIT:

The original submission by the registrant was made on January 23, 1984. The study submitted was:

IRRITANT EFFECTS OF CL 11.344/69 WP 50 (Tough^{R} 45 WP) ON RABBIT EYE MUCOSA, Kynoch, S., Huntingdon Research Centre, March 8, 1978.
The conclusion from the study was that the compound gave a positive test for eye irritation, according to the definition given in the Code of Federal Regulations. The eyes of all six animals were normal by day seven.

The study was assigned accession number 72340, reviewed, and classified as Core-minimum on June 9, 1986.

O-6 81-5 PRIMARY DERMAL IRRITATION:

On January 23,1984 the following study was submitted by the registrant:

IRRITANT EFFECTS OF CL 11.344/69/WP 50 (Tough^{R} 45 WP) ON RABBIT SKIN, Study number 8906/22D/78, S. Kynock, Huntingdon Research Centre, June 28,1978.

The results indicated that none of the animals showed any observable response to treatment throughout the 72 hour observation period. The primary irritation index was calculated

as 0. Tough® 45 WP is not considered to be an irritant to rabbit skin.

Upon review of additional data the study was classified as Core-Minimum by the Agency on June 9, 1986.

O-7 81-6, DERMAL SENSITIZATION:

A total of 4 dermal sensitization studies have been conducted on Pyridate compounds and formulations: 1) purified Pyridate, 2) Pyridate technical, 3) Tough® 45 WP, and 4) Tough® 3.75 EC. The results of each study indicated that Pyridate and formulations of Pyridate are sensitizers in albino guinea-pigs. The statement "This product may cause sensitization in some individuals" will be added to the label.

O-8 82-1, 90 DAY FEEDING, RAT:

The original study submitted 1/23/84 was classified as supplemental. The study was re-run and submitted 4/6/87. Upon review the new study was classified as core guideline, MRID number 40157401, with NOEL of 62.5 mg/kg/day and an LEL of 177 mg/kg/day.

O-9 82-1, 90 DAY FEEDING, DOG:

The original study was submitted to the Agency on 1/23/84. It was reviewed and classified as core supplemental on 3/20/86. Additional data was submitted and reviewed on 8/20/86, but was insufficient to re-classify the study. The study was re-run and submitted to the Agency on 2/27/87. MRID number 40101604 was assigned and the new study was reviewed and classified as core guideline on 7/14/87.

O-10 83-1, Chronic Feeding, Rat:

The original study, submitted 1/23/84, accession number 72342, was reviewed and classified as core supplemental by the agency on 7/8/86. The deficiencies were addressed in a supplemental data package which was submitted to the Agency on 10/23/87. The supplemental data addresses all of the deficiencies listed in the review of 6/29/86 and is believed by the registrant to be sufficient to re-classify the study.

O-11 83-1, Chronic Feeding, Dog:

The original study, submitted 1/23/84, accession number 72344,

was reviewed by the Agency and classified as invalid on 4/15/86. After careful review the registrant agrees with the Agency's findings. A new 12-month dog study was initiated on 8/11/87 and is now running at Hazleton Laboratory, Vienna, Virginia. The final report is due 3/89. An interim report can be made available to the Agency, if desired.

O-12 83-2, Oncogenicity, Rat:

The original study was submitted to the Agency on 1/23/84, and assigned accession number 72343. The oncogenicity and chronic feeding, rat, was a combined study. Please see comments on the chronic feeding rat study as they relate to both.

O-13 83-2, Oncogenicity, Mouse:

The original study was submitted 1/23/84. It was assigned accession number 72346, reviewed, and classified as supplemental by the Agency on 10/5/86. It was indicated that the study could be upgraded to core-minimum if listed deficiencies were resolved. TNO Laboratories, the original producer of the study, is currently preparing supplemental data to address the indicated deficiencies. The expected completion date is 2/88.

O-14 83-3 Teratogenicity, Rat:

The original study, submitted 1/23/84 was reviewed by the Agency and classified as core-supplemental on 5/18/84. Additional data was submitted but was not sufficient to re-classify to core-minimum. The study was re-run and submitted 5/86 for review. It was assigned accession number 262546 and classified as core-guideline in the Agency's review of 8/20/86.

O-15 83-3, Teratogenicity, Rabbit:

The original study was submitted on 1/23/84. It was assigned accession number 72348, reviewed and classified as core-supplemental by the Agency on 12/5/86. A second study, accession no 259948, was submitted 10/14/85. It was reviewed 6/9/86 and also classified as core-supplemental. A third study, started fall 1987, was submitted to the Agency on 12/14/87. This study demonstrates maternal toxicity and has a NOEL of 150 mg/kg/day and an LEL of 300 mg/kg/day. There were no observed compound related teratogenic effects.

O-16 83-4, Multigeneration reproduction, Rat:

The original study was submitted to the Agency on 1/23/84. It was reviewed, assigned accession number 72347 and classified as core-

supplemental on 12/5/86. The Agency indicated in the review that the study could be up-graded to core-minimum if deficiencies were corrected. The originator of the study, TNO, Netherlands, currently is preparing a response. Supplemental information will be available 2/88.

0-17 84-2, Battery of Mutagenicity Tests:

Gilmore submitted a battery of 6 mutagenicity tests on 1/23/84 to satisfy the mutagenicity testing requirement. In their review of 3/14/86, accession number 72348, the Agency found all but one of the studies unacceptable and recommended repeating the others. Gilmore has conducted additional studies and has satisfied the requirements of Gene Mutation, and Structural Chromosomal Aberration groups. A new Bacillus subtilis study intended for the Other Genotoxic Effects group was rejected for failure to show toxicity. This was caused by the limited solubility of the compound. A new study is currently underway at Hazleton Laboratories, Netherlands, using a modified protocol with suspension technique. This study will be completed December 1987 with the final report submitted 1/88. The study will meet EPA requirements.

It should be pointed out that even though some of the mutagenicity tests did not meet EPA's strict guidelines, none demonstrated any evidence of a mutagenic effect. This fact was commented upon by Dr. David Brusick, Hazleton Laboratories, a recognized authority on mutagenic effects, in a submission by Gilmore to the Agency on 9/19/86.

O-19 71-1, Avian Oral LD50, Bobwhite:

The original study was submitted to the Agency on 1/23/84. It was assigned accession number 72350 and reviewed on 9/30/85. The study was found unacceptable. A new study was commissioned and the final report received 5/2/86. It was submitted to the Agency on 10/9/86. Additional copies of the study were requested by the Agency on 10/1/87. Acknowledgement of the additional copies was made on 10/21/87 and MRID number 40373201 was assigned. An expedited review has been promised by the Agency. It should be noted that the results of the second study, LD50 = 1023 - 1577 mg/kg (95% confidence limits) were well within the results of the original study of LD50 = 1505 mg/kg (1204 - 1803 mg/kg, 95% confidence limits).

O-20 71-2, Avian Dietary LC50, Mallard Duck and Bobwhite:

The following two studies were submitted to the Agency on 1/23/84:

1. A DIETARY LC50 STUDY IN THE BOBWHITE WITH PYRIDATE, Project No 190-101, J. Beavers, Wildlife International, 1984.
The dietary LC50 value of Pyridate in the bobwhite was determined by inspection to be greater than 5000 ppm.

2. A DIETARY LC50 STUDY IN THE MALLARD WITH PYRIDATE, Project 190-102, J. Beavers, Wildlife International, 1984.
The dietary LC50 value of Pyridate in the Mallard was determined by inspection to be greater than 5000 ppm.

The studies were assigned accession number 72350, reviewed on September 30, 1985, and accepted as fulfilling the requirement for Avian LD50 in wild waterfowl and upland fowl species.

O-21 71-4, Avian Reproduction, Mallard Duck and Bobwhite:

The final reports for both studies have been received and are a part of this registration submission.
The results show that for the bobwhite there were no treatment related effects upon adult birds exposed to dietary concentrations of 256, 640 or 1600 parts per million (ppm) Pyridate technical. No treatment related effects upon reproductive performance were noted. The no-observed-effect concentration for bobwhite in the study was 1600 ppm, the highest level tested.
For the mallard duck there were no overt signs of toxicity or mortalities among adult birds exposed to dietary concentrations of 256, 600 or 1600 ppm Pyridate technical. No treatment related effects upon reproductive parameters were noted at 256 or 600 ppm concentrations. While not statistically significant, there appeared to be a slight reduction in hatchability at the 1600 ppm concentration. The no-observed-effect concentration for mallards in the study was greater than 640 but less than or equal to 1600 ppm.

O-22 72-1, Freshwater Fish LC50, Rainbow Trout and Bluegill:

The following 2 studies were submitted to the Agency on October 17, 1986:

1. ACUTE TOXICITY OF PYRIDATE TECHNICAL TO RAINBOW TROUT, J. Bowman, Study number 34819, Analytical Bio-Chemistry Laboratories, Inc., August 26, 1986.
Results of the study indicated that the LC50 to trout was >1.2 ppm.

2. ACUTE TOXICITY OF PYRIDATE TECHNICAL TO BLUEGILL SUNFISH. J. Bowman, Study number 34303, Analytical Bio-Chemistry Laboratories, Inc., August 26, 1986.
Results of the study indicated that the LC50 to bluegill was >2.1 ppm.

The studies were assigned accession numbers 265681 and 265682 and reviewed by the Agency on January 5, 1987. The studies were accepted as fulfilling guideline requirements for warmwater and coldwater fish.

O-23 72-1, Acute LC50, Daphnia:

The following study was submitted to the Agency on 1/23/84:

ACUTE TOXICITY OF PYRIDATE TECHNICAL TO DAPHNIA MAGNA, Project 009178, RCC, July 6, 1982.
The results of the study indicated that the LC50 estimation for a 48 hour exposure of Daphnia magna to Pyridate technical is 1.09 ppm with a 95% confidence interval of 1.02 - 1.15 ppm. The LC20 and LC80 are estimated to be 0.81 and 1.45 ppm respectively.

The study was assigned accession number 72350, reviewed, and classified as supplemental on May 18, 1984.

With the submission of additional data, accession number 264614, the study was reviewed by Daniel Rieder on April 28, 1987 and upgraded from supplementary to core-guideline.

O-24 72-3, Acute LC50, Marine Fish:

The study was submitted to the Agency on November 29,1984. It was assigned accession number 73281 and reviewed on April 18,1985. The study was found not scientifically sound because the test vessels were agitated and not analyzed. The main concern was that if the compound was volatile it would be lost from the vessels upon agitation. A discussion with the Agency indicated that if it can be shown that the compound was not volatile the study could

probably be salvaged.
A new study was conducted to show the volatility and solubility of Pyridate in sea water. The test vessels were of the same size of those used in the original test and were agitated in the same manner. The solubility of Pyridate in sea water is approximately 0.3 ppm at 20 degrees C. The solutions never reached constant equilibrium because of two competing factors: 1) adsorption of Pyridate to the glass walls of the containers, and 2) hydrolysis of Pyridate to CL-9673. However, the material balance of greater than 96% clearly indicates no volatilization of Pyridate. It is also clear that at an attempted target of 1000 ppm, the highest test concentration, the fish were exposed to a saturated solution of Pyridate. There were no fatalities at any of the test concentrations, including 1000 ppm.
A copy of the study, SOLUBILITY AND VOLATILITY STUDY OF 14C-PYRIDATE IN SEA WATER, Project 8712, A. Zohner, Chemie Linz, October 1, 1987, is enclosed with this submission.

0-25 72-3, Acute LD_{50} Embryo-larvae:

Study submitted 8/14/87. Received by the agency and assigned MRID No. 40303801. Study currently under review.

0-26 72-3, Acute LC_{50} Marine shrimp:

Study submitted 11/29/84. Assigned accession number 73281. Approved by the agency 4/29/85. LC_{50} = 4ppm (3.5-5.1) considered moderately toxic to marine shrimp.

0-27 141-01, Acute contact honey bee:

LD_{50} honey bee study submitted to the agency 10/9/86. Additional copies were requested 10/1/87. Study resubmitted 10/8/87. The agency acknowledged receipt of the second submission and assigned MRID No. 40373202. The study is currently in scientific review.

0-28 171-2, Chemical Identity:

Please see 61-1 and 61-3, Product Chemistry.

0-29 171-3, Directions for use:

A label was submitted in the original data package of 1/23/84. Accession number 72353. However, new updated labels are submitted with this application.

0-30 171-4, Nature of residue, plants:

Plant metabolism studies were submitted in support of the EUP registration for this product on 1/23/84, accession number 72351; and on 1/17/85, accession number 73282. However, three new metabolism studies:

1.) METABOLISM OF PYRIDATE AND CL-9673 IN BROCCOLI.
2.) METABOLISM OF PYRIDATE AND CL-9673 IN PEANUTS.
3.) METABOLISM OF PYRIDATE AND CL-9673 IN CORN.

are complete and final reports will be submitted to the Agency the week of January 11, 1988. The results of those studies confirm that the compounds of toxicological concern are Pyridate and its hydrolysis product CL-9673.

O-31 171-4, Residue Analytical Method:

In the original data submission of 1/23/84, four analytical methods were provided. The data was assigned accession number 72351, and accepted in Garbus' review of 10/7/85.

A simplified analytical method was provided to the Agency on 10/12/87 and assigned MRID number 40374801. The method is currently under review.

O-32 171-4, Magnitude of residues, crops:

The original submission was made to the Agency 1/23/84, and assigned accession number 72351. Upon review of that submission the Agency asked for additional data. The additional residue data was submitted on 5/9/85 and assigned accession number 73597. The Agency concluded from the data that, as indicated by the registrant, no residues occurred at harvest. The Agency accepted the data but indicated that additional residue data from all major crop producing areas would be requested.

The registrant has conducted additional studies, from all major crop producing areas, for corn wheat, cabbage, alfalfa, and grain sorghum. The field portion of these studies is complete and analysis is currently under way.

It is the registrant's opinion that sufficient data currently exists to support the position that no residues will occur on any of the petitioned crops when application is made according to label directions.

O-33 171-6, Proposed tolerance:

A tolerance proposal is included with this submission. It

proposes a tolerance of 0.03ppm on all RAC's and feed. This is being proposed because there are no detectable residues in any RAC's above the level of detection for the latest analytical method, which is 0.03ppm.

0-34 171-7, Reasonable grounds for support:

Reasonable grounds for support are contained in the enclosed benefits package.

0-35 171-13, Analytical standards:

Unlabeled PAI has been submitted to EPA Labs, Beltsville, and EPA Depository, RTP. Samples of radio labeled analytical grade standards will be provided upon request.

0-36 161-1, Hydrolysis:

The original submission was made to the Agency on 1/23/84. The study, DETERMINATION OF THE HYDROLYSIS OF PYRIDATE (CL 11.344) IN WATER AS A FUNCTION OF PH, A Zohner,et al, Report No 735, September 1981, was assigned accession number 72352 and reviewed on 5/21/84. The study was accepted as satisfying the data requirement.

0-37 161-2, Photodegradation Water:

The original study was submitted to the Agency on 1/23/84 and assigned accession number 72352. In their letter of 10/1/87 the Agency requested additional copies of the study which were submitted by the registrant on 10/08/87. MRID number 40373203 was assigned and the study is currently under review.

0-38 161-3, Photodegradation Soil:

The original study was submitted 11/29/84. It was assigned accession number 73283 and reviewed by the Agency 1/30/86. Deficiencies were determined to exist and were listed. All deficiencies are addressed in a report that is included in this submission.

0-39 162-1 Aerobic Soil Metabolism:

The original study was submitted 1/23/84. It was assigned accession number 72352 and found to contain deficiencies in the Agency's review of 5/10/84. It was replaced by a new study,

AEROBIC SOIL METABOLISM STUDY OF 14C-CL9673, THE MAIN METABOLITE OF 14C-PYRIDATE, IN SOIL, Report No 832, submitted 2/25/86. Accession no 261827 was assigned and the new study was accepted by the Agency as fulfilling the aerobic soil metabolism requirement.

O-40 162-2, Anaerobic Soil Metabolism:

A new study ANAEROBIC SOIL METABOLISM STUDY OF 14C-CL9673, THE HYDROLYZATION PRODUCT OF 14C-PYRIDATE, has been completed and is a part of this submission.

O-41 163-1, Leaching and Adsorption/Desorption:

Gilmore submitted four studies to the Agency on 2/25/86. Accession number 261827 was assigned to the data and it was reviewed by the Agency on 5/13/86. The studies were accepted, but additional data was requested. After an extensive review of existing and new data, the registrant believes sufficient data has been submitted to satisfy this requirement. A request to the Agency to reconsider the data is a part of this submission.

O-42 164-1, Soil Dissipation, Field:

Four soil dissipation studies conducted in different geographic areas of the country have been completed. Final reports on those studies are a part of this submission.

O-43 165-1, Confined Rotational Crops:

The original data submission, submitted 1/23/84, was assigned accession number 72352 and reviewed by the Agency 5/21/84. The study was rejected because it was conducted in foreign soil. A second study, CONFINED ACCUMULATION STUDIES ON ROTATIONAL CROPS WITH 14C-PYRIDATE, A Zohner, July 1985, was assigned accession number 264980 and reviewed by the Agency on 12/24/86. It was also rejected.
A request to have the Agency reconsider the data is included in this submission. The registrant feels the data contains sufficient information to satisfy the Agency's concerns.

O-44 165-2, Rotational Crops, Field:

Based on the confined rotational crop data the registrant feels that there is no need for field rotational data. A request to the Agency to waive this requirement has been prepared and is a part of this submission.

O-45 165-4, Accumulation in Fish:

The original study was submitted 1/17/85, and assigned accession number 73283. It was accepted by the Agency as satisfying the requirement on 2/11/86. Please note, a BCF of 464 in whole fish was referenced in Mr. R. Taylor's letter of approval of 2/11/86. However, this is an error as the study author indicated a BCF in whole fish of 116.